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PANTOTHENIC ACID IN NUTRITION

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Introduction

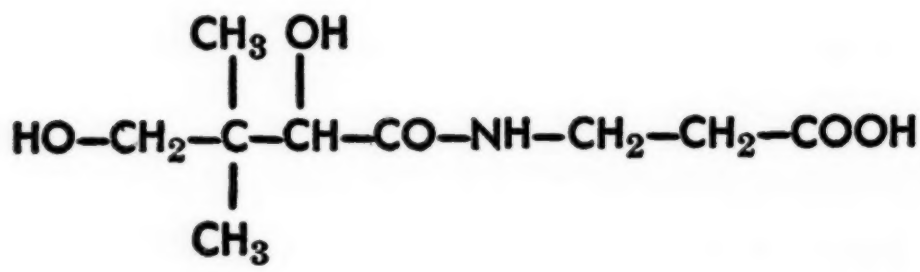
Although vitamins are generally thought of as compounds essential for animals, including man, it should be appreciated that several of these important biological substances were first discovered and studied as growth factors for microorganisms. So it is with pantothenic acid.

Dr. Roger J. Williams et al in 1933 (1) reported on an acidic substance which was required as a growth factor for yeast. Because this substance had such a universal distribution in biological material it was named "pantothenic acid" which means literally, "from everywhere." Writing of his earlier research experiences, (2), Dr. Williams presents a lucid description of the fundamental role that the substance, later identified as pantothenic acid, plays in the growth process. "I remember clearly the first single yeast cell I isolated. I was to isolate thousands in my later work, but none made the impression that this one did, because it was then a chore to isolate it and its behavior was unexpected. It was a perfectly good looking, plump but not overly obese yeast cell and it was suspended in a synthetic medium in which the yeast en masse seemed to grow with appreciable enthusiasm. Once I had it in focus under the microscope, I watched it hour by hour. Nothing happened: I concluded that it was a slow starter. I found a means of spotting it on a slide and put it in an incubator overnight, expecting the next day to find a cluster of yeast cells. The next day it was quiescent (and remained so for the several days that I watched it) as if it had been put to sleep. As I subsequently watched other yeast cells in similar media, I found that some single cells would grow a little and some wouldn't at all, but that they would all grow to clusters like bunches of grapes if even a little decoction of yeast was added, the hanging droplets would be filled with thousands of yeast cells." Needless to say the outstanding active ingredient in the "decoction" was subsequently shown to be pantothenic acid.

The first concentrates of pantothenic acid prepared from liver were known variously as the "filtrate factor," because the active principle was not retained on the absorbent fullers earth, and as the "chick antidermatitis factor" since the preparation was shown to be effective in preventing and curing a characteristic dermatitis in chicks but not in rats. In addition, it was soon demonstrated that a concentrate of the filtrate factor served as a growth factor for rats.

A clue to the structure of the vitamin came from the observation that the chick antidermatitis factor was destroyed by alkali and that β-alanine could be isolated from the reaction (3). The resemblance was noted also between the crude factor needed by chicks and rats and the yeast factor, called pantothenic acid by R. J. Williams. The isolation of the vitamin in pure form was followed shortly by the establishment of its chemical structure (Fig. 1) and synthesis (4).

FIGURE 1. Pantothenic Acid



The presence of a "peptidic bond" in pantothenic acid explains why it is one of the most unstable members of the B complex group of vitamins. The pH of solutions of this vitamin must be kept near neutrality as it is readily hydrolyzed under acidic or alkaline conditions.

Effects of Pantothenic Acid Deficiency in Animals

The literature reports on the signs giving evidence of pantothenic acid deficiency are far too numerous to be presented here in any detail. The mass of experimental observations have been conveniently summarized by Novelli as follows (5):

1. Failure to grow; loss of weight; sudden death.
2. Lesions of skin, hair or feathers.
3. Lesions of the nervous system.
4. Inhibition of antibody formation.
5. Lesions of the adrenal glands.

Pantothenic Acid and Growth

The importance of pantothenic acid in the growth process cannot be emphasized too greatly particularly for the very young and rapidly growing animal. It is most interesting to note, however, that as the animal (rat) matures and approaches adulthood the requirement for the vitamin is markedly reduced. In an effort to study this point further, Krehl (6) has recently conducted experiments on pantothenic acid deficient rats that have been first hypophysectomized (pituitary glands removed) and hence deprived of a source of growth hormone (also other trophic hormones). Such animals,

when placed on the pantothenic acid deficient regimen fail to exhibit the usual eventful course of the deficiency which terminates in death after 5 to 6 weeks. Instead, they live for long periods of time as immature, non-growing rats that retain the characteristic soft "youthful hair" of the hypophysectomized animal. The important point to note is that here the impetus to grow has been removed and with it a marked reduction in the apparent need for pantothenic acid. One cannot help but recall here the hanging drop experiment with the yeast which failed to grow noted many years ago by R. J. Williams. One might well ask whether the difficulty of producing pantothenic acid deficiency in the adult human might not be related to a reduced need for this vitamin in the mature, non-growing individual?

Pantothenic Acid and Skin Changes

Pantothenic acid deficiency has long been associated with dermatitis of the skin and greying of the hair or feathers. This evidence of lack of this vitamin has been much complicated by concomitant deficiencies of other B complex vitamins, particularly biotin, folic acid and inositol. The greatest complication and harm resulting from these early observations was the premature, over-enthusiastic, unjustified and futile attempts to cure the greying of hair in human subjects.

Although the involvement of the adrenal glands in pantothenic acid deficiency will be discussed more extensively, the work of Ralli et al (7) on the relationship between adrenal activity and pantothenic acid deficiency deserves mention. As indicated above, pantothenic acid deficiency in experimental animals, such as the rat, is evidenced by a decreased concentration of melanin pigment in the hair apparatus. If such a deficient rat is now adrenalectomized, an almost complete reversal of the pigment loss takes place and hair color is restored. Ralli and Dumm state: (8) "That the adrenocortical hormones are involved in this reaction is shown by the fact that the stimulating effect of adrenalectomy on melanin deposition and hair growth was suppressed when the animals received DCA (desoxycorticosterone acetate) by injection following adrenalectomy." In further support of the above concept, it is known (9) that hypophysectomy produces an atrophy of the adrenal cortex and is associated with an increase in pigmentation in black rats.

Nerve Function and Pantothenic Acid

Signs of nervous system involvement in pantothenic acid deficiency are quite clear as indicated by the following selected observations: the characteristic goose step or abnormal gait in pigs suffering from pantothenate deficiency reported by Wintrobe (10); the spinal cord lesions reported by Phil-

lips and Engel (11) in chickens given a pantothenic acid deficient diet; and the curious gradual loss of control of the rear legs in severely pantothenic acid deficient rats (6).

Clinical observations on human subjects have indicated a possible relationship between the so-called "burning feet syndrome" as seen particularly in diet-restricted prisoners-of-war, and pantothenic acid deficiency. This syndrome appears to be a distinct entity and apparently is of nutritional etiology; in fact it has been called "nutritional melalgia" (12, 13). This disease in its milder form is characterized by an onset of bilateral paresthesias affecting the lower extremities and as the condition progresses patients complain of severe shooting pains which appear to be aggravated by exertion or warmth and alleviated by cold. In the most advanced forms, the patients are extremely sensitive to such minor stimuli as floor vibrations. The syndrome as observed does not involve prominent muscle wasting or paralysis. While investigators have not obtained any response of this disease from thiamine or niacin, pantothenic acid has been used with favorable and often dramatic results. Clinicians dealing with the syndrome have reported that whenever the general quality of the dietary is improved there is a general alleviation of pain in the affected feet.

Pantothenic Acid and Antibody Formation

Early studies on the effects of vitamin deficiency on infection and susceptibility to infection indicated that pantothenic acid deficient rats were less susceptible than normal rats to infection with type 1 pneumococcus (14) and that pantothenate deficient mice were more resistant than the normal animals to the Theilers strain of encephalomyelitis virus but not to the Lansing strain of poliomyelitis virus (15).

In a recent series of well conceived and executed experiments, Axelrod et al (16) have provided excellent evidence to show that pantothenic acid is involved in the synthesis of antibodies. From the results of their work, pantothenic acid does not seem to function in the mere release of preformed antibodies, nor does the deficiency of the vitamin result in increased antibody destruction; neither does this effect of pantothenic acid on antibody formation seem to be operative through the adrenal glands since injected adrenal cortical extract did not influence antibody titres in normal or deficient animals.

Pantothenic Acid and the Adrenal Gland

One of the most fascinating aspects of the biological role of pantothenic acid is its relationship to the function of the adrenal glands. Since the first observation of Morgan and Sims (17) that the adrenals of rats on diets de-

ficient in the "filtrate factor" showed definite pathological changes, evidence has accumulated that pantothenic acid is of great importance in maintaining the integrity and normal function of the adrenals. The lesions of the adrenals of pantothenate deficient rats studied in detail by Deane and McKibbin (18) are characterized first by a loss of lipid material from the cortex of the gland which also is rapidly depleted of ketosteroid material. This is followed by a steady deterioration of the adrenal cortex with gradual development of areas of necrosis, followed by hemorrhage, with eventual fibrous infiltration. At autopsy the gross picture in the pantothenic acid deficient rat is as follows: the thymus is atrophic; the adrenal is enlarged and mottled or solid black in color, and there is a marked reduction of fat everywhere, but particularly noticeable in the abdomen and around the kidneys. The adrenals are often so hemorrhagic that they have been aptly described as "bags of blood."

By placing lactating females on a pantothenic acid free diet immediately after giving birth to their litters, Schultz et al (19) were able to produce a profound pantothenic acid deficiency in the young in a few days after weaning with all of the characteristic signs of the deficiency mentioned before. Since the conditions of this experiment enhance the stress placed on the deficient animals, the rapid development of the deficiency signs with respect to the adrenal gland emphasizes further the critical importance of pantothenic acid to the normal functioning of the adrenal gland and the synthesis of cortical hormone. This concept was given further support by the added observation (19) that the administration of ACTH (adrenocorticotrophic hormone) produces a marked magnification of the lesions. Histologically, many of the adrenal glands from ACTH treated-pantothenic acid deficient animals show few if any remaining cortical cells intact. The massive hemorrhage choking the cortex often involves the medulla as well. Just as ACTH magnified the signs of adrenal damage in pantothenate deficient animals, cortisone exerted a protective influence on the adrenal (19). Deficient rats treated with cortisone presented a picture practically indistinguishable from that of normal control animals treated with this hormone.

From the above considerations, a tentative hypothesis has been put forward (20) to explain the mechanism of the development of adrenal damage in pantothenic acid deficiency in the rat.

At weaning the young rat has a good supply of the functional form of pantothenic acid in its adrenal cortex, but early in the deficiency this level is depressed, although the pantothenic acid in the peripheral tissues may still be normal or nearly so. As the level of pantothenic acid containing enzyme falls, the synthesis of adrenal corticoids is depressed and as the concentration of circulating cortical hormone falls, the pituitary is stimulated to produce more of the trophic hormone, ACTH. The debilitated adrenal gland is, how-

ever, unable to respond to this increased stimulus and hence a vicious cycle is initiated and perpetuated. Under excessive ACTH secretion, the adrenal gland hypertrophies morphologically and atrophies functionally, in a manner somewhat analogous to the status of the thyroid gland in subjects receiving certain goitrogens. The reduction in circulating adrenal cortical hormone and the subsequent effect on increased ACTH production may be aided and abetted to an undetermined degree by the stressful circumstances imposed by the deficiency of pantothenic acid alone. As the adrenal gland hypertrophies in its vain effort to produce an adequate supply of cortical hormone under the continual "pounding" of excessive ACTH, hemorrhagic necrosis develops.

Certain corollaries derive from this hypothesis. First, ACTH should exacerbate the severity of the lesions in the deficient animals, while cortisone on the other hand should spare the gland from hemorrhagic necrosis by blocking or inhibiting excessive ACTH secretion. It must be emphasized however that cortisone treatment will not protect the life of the animal, since pantothenic acid deficiency in the peripheral tissues will continue and eventually produce a fatal outcome. The experimental evidence reviewed above has greatly strengthened the validity of the hypothesis set forth.

Physiological Evidence of Adrenal Insufficiency in Pantothenic Acid Deficiency

A variety of experiments by workers in several laboratories (8, 20, 21) have shown rather conclusively that pantothenic acid deficiency in experimental animals is accompanied by various physiological and biochemical responses to different kinds of stress.

Most of the experiments have attempted to provide some answers to the following fundamental questions: (a) can the pantothenic acid deficient rat synthesize and secrete adrenal steroids? and (b) does pantothenic acid deficiency prevent the utilization of adrenal corticoids in the peripheral tissues? Because of the extreme technical difficulty of measuring adrenal hormones directly particularly in small animals, indirect changes or indices have to be measured which can only reflect alterations in adrenal corticoid secretion and utilization. The principle indices that have been studied are as follows: (a) determination alterations in the white cell counts (i.e.) (alterations of eosinophile and lymphocyte counts); (b) changes in carbohydrate metabolism, such as measurement of the fasting blood glucose, insulin sensitivity, glucose and nitrogen excretion after phloridzination, and hepatic glycogen deposition in the fasting state, and (c) alterations in the adrenal ascorbic acid or cholesterol levels in normal and pantothenic acid deficient animals in both stressed and non-stressed states.

In the experiments conducted by Winters et al (22) the functional capacity of the adrenal cortex and the ability of the peripheral tissues to utilize the cortical hormone was determined in groups of both control and deficient animals after 5-6 weeks on the experimental diets tested either without hormone treatment (i.e. before or after treatment with ACTH or cortisone). Since the details of these experiments have been presented (22) the results may be summarized as follows: (a) pantothenic acid deficient animals showed a lack of adrenal cortical function in those phases of activity usually attributed to the 17 hydroxy, C-11 oxysteroid hormone (cortisone and/or compound F). For example, after stress, pantothenic acid deficient animals failed to exhibit the customary sharp drop in the number of white cells (eosinophiles and lymphocytes); were much more sensitive to insulin than normal rats; had an inability to excrete normal amounts of glucose and nitrogen after treatment with phloridzin; and were unable to deposit the usual quantity of glycogen in the liver in the fasting state.

Although the administration of ACTH failed to influence the evidence of adrenal insufficiency in the deficient animals, the normal response to this hormone was obtained with control animals. The administration of cortisone on the other hand was observed to correct the defect in the deficient animals.

It seems reasonable to consider from these results and those of a similar nature reported by other laboratories (8, 21) that the essential block in the pantothenic acid deficient rat as far as the adrenal gland is concerned is in its inability to synthesize an adequate supply of adrenal hormone and not in a failure of the peripheral tissues to utilize the hormone.

Although blood cholesterol levels of pantothenic acid deficient animals are not altered significantly as compared to the normal, there is a significant fall in the adrenal cholesterol level. Because of certain technical difficulties and differences in the degree of pantothenic acid deficiency, changes in the adrenal ascorbic acid level are much more difficult to interpret. Ralli has quite properly stated (8) that "the significance of analyses of adrenals from severely deficient animals with the accompanying inanition and superimposed infections is subject to question."

Studies by Ralli et al which demonstrated that large doses of pantothenic acid markedly increased the time that both intact and adrenalectomized rats could swim in cold water led to more extended studies in man (23). Normal men used as experimental subjects were immersed in water at 9°C for 8 minutes. Blood and urine samples obtained before and after the stress were analyzed for certain of the constituents known to be influenced by adrenal cortical function. The subjects acting as their own controls were given 10 gm. of pantothenic acid each day for 6 weeks and were tested again as indicated above. An analysis of the data indicate in general that the large doses of

pantothenic acid exerted a significantly protective action against the rather severe stress imposed.

Discovery and Nature of the Pantothenic Acid Coenzyme

As indicated before, pantothenic acid was long known as a growth factor for numerous microorganisms and this fact provided a tool for evaluating its distribution in natural products. It was soon found that assay values for pantothenic acid obtained with chicks were considerably higher than those obtained by microbiological assay methods. This discrepancy added confirmation to early recognition of the fact that pantothenic acid existed in tissues in a so-called "bound form." Various efforts to liberate this bound form of the vitmain by the application of a number of enzymes, particularly phosphatases, led to microbiological assay values that are now recognized as being much too low. The abundant distribution of this vitamin did however imply for it a vital part in metabolism.

The discovery of the biochemical function of pantothenic acid was not long in coming. Although it is almost certain that the magnitude of the importance of this "key" to the metabolism of so many substances was not appreciated for some time, even to its discoverers. The unfolding of the metabolic role of this vitamin was, as Lipmann so engagingly states (24), assisted by "a number of fortunate accidents" — the first, as the result of the study of a seemingly unimportant reaction, the acetylation of sulfanilamide by pigeon liver tissues. In this study, Lipmann noted (25) that a cell-free preparation of pigeon liver, when allowed to respire, would acetylate considerable amounts of sulfanilamide. Anaerobically, little acetylation occurred unless ATP was added. When the tissue was allowed to autolyze no sulfanilamide was acetylated aerobically, although such an inactivated preparation could be reactivated by additions of boiled liver juice. This suggested that a heat-stable co-factor was involved and that the acetylation reaction probably consisted of an apoenzymecoenzyme complex with ATP as the energy factor. The first attempts to identify a vitamin as part of this coenzyme failed since pantothenic acid so bound does not stimulate the growth of the usual test organism, *L. arabinosus*. Guirard ingeniously observed (26) however, that if the coenzyme was first hydrolyzed with acid, a substance was liberated which stimulated yeast growth. This substance, identified as β-alanine, provided the clue which soon led to the identification of pantothenic acid in the coenzyme, which was named "*coenzyme A*" or CoA *(A for acetylation)*. Lipmann and Kaplan (27) recognized the similarity of their acetylation system to one described by Nachmansohn and his collaborators in brain tissue which acetylates choline to form the biologically important, acetyl cho-

line (28). The brain enzyme system, inactivated by dialysis or autolysis, was found to be reactivated by additions of purified coenzyme A.

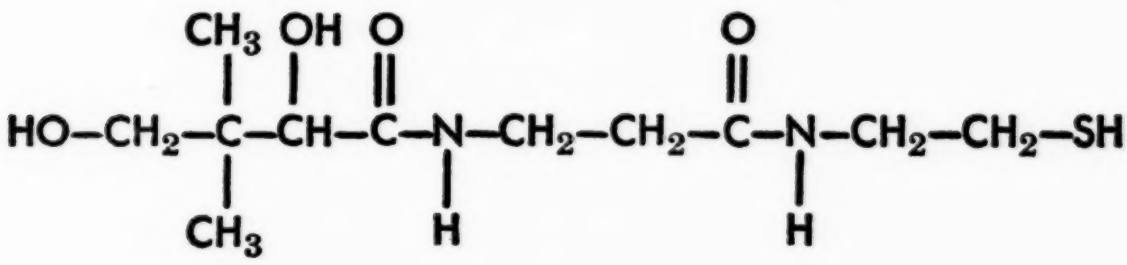
Meanwhile, the long standing puzzle of the bound form of pantothenic acid was quickly solved by the development of a method (29) for the total liberation of the vitamin from the coenzyme A in biological materials by first treating the sample with alkaline phosphatase, then with a pigeon liver enzyme.

Novelli et al (30) applied this treatment procedure to a number of animal tissues to determine their content of bound pantothenic acid as CoA. They observed that most, if not all, of the pantothenic acid in tissues is there in the form of CoA and that next to liver the adrenal gland has the highest concentration of the coenzyme.

Other Bound Forms of Pantothenic Acid

Williams et al (31) described a new growth factor called *LBF* needed for the growth of the lactic acid bacillus, *L. bulgaricus*. This initial observation proved important because it led to subsequent work which contributed materially to the final elucidation of the structure of CoA. The chemical studies conducted on the LBF revealed the fact that it is a compound containing pantothenic acid linked to a sulfur containing group. This substance was called pantetheine (32) and has the following structure (Fig. 2).

FIGURE 2. Pantetheine



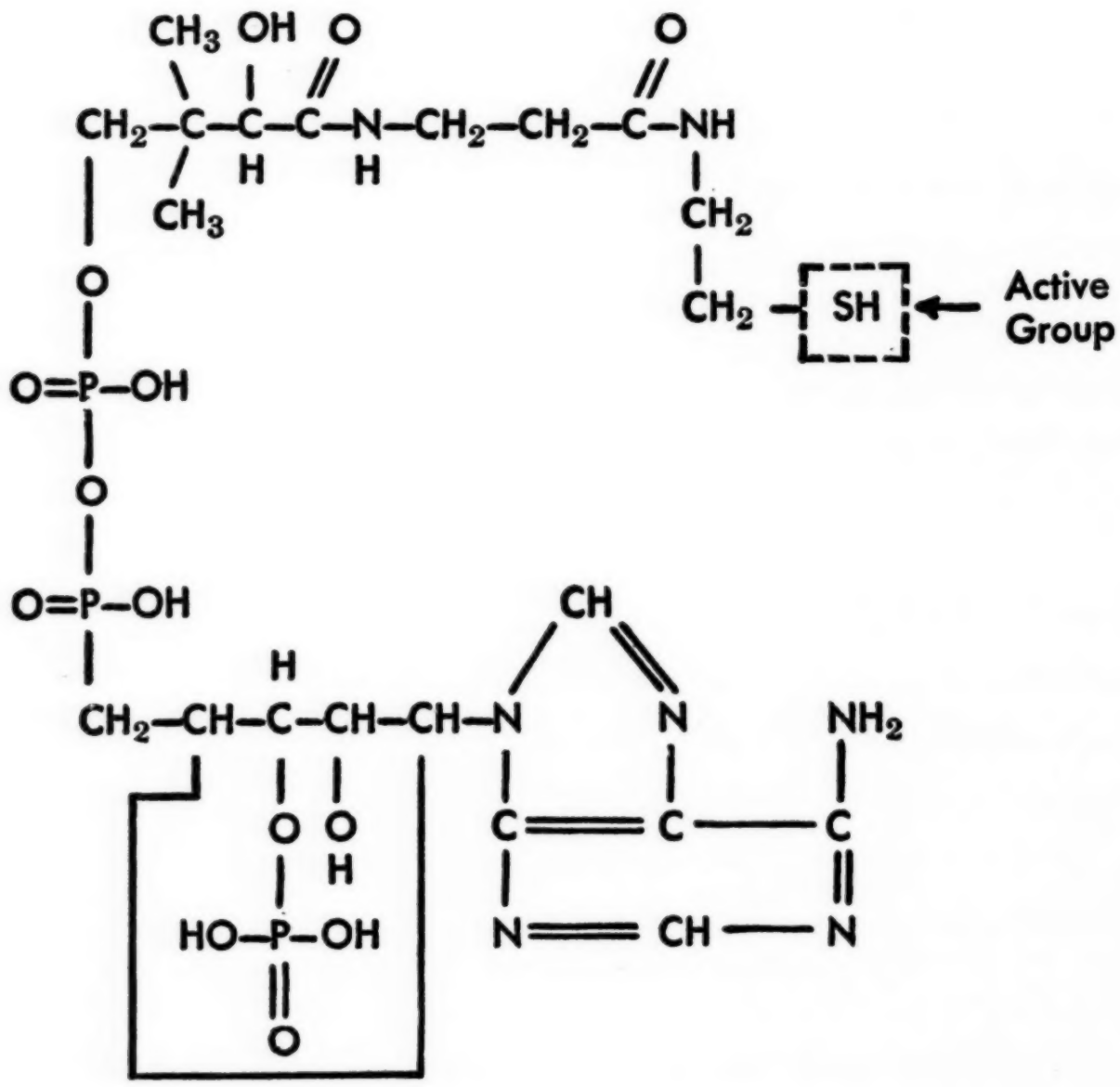
This product is important because it is a breakdown product of Co A and is also an intermediate in its biosynthesis.

Another bound form of pantothenic acid of interest is called "pantothenic acid conjugate" which was shown by King et al (32) to be a growth factor for *Acetobacter suboxydans*. Although the exact structure of this factor is in doubt, it is probably similar to phosphopantetheine. It is worthy of note that while pantothenic acid, pantotheine and pantothenic acid conjugate can serve as growth factors for various organisms, only CoA serves as the biochemically active form of pantothenic acid.

The Structure of CoA — "Active" Acetate

Although the details concerning the elucidation of the structure of CoA comprise a brilliant chapter in modern biochemistry, it must suffice here to say that the structure of CoA has been established by enzymatic degradative procedures and by biosynthesis from pantetheine which is presumed to be derived from pantothenic acid (Fig. 3).

FIGURE 3. Structure of CoA

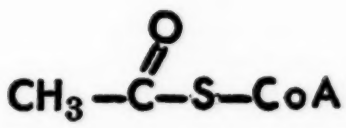


To make clear the manner in which Co A functions, one must consider another aspect of metabolism which has long puzzled biochemists, namely the mechanism whereby the 2 carbon fragments resulting from fatty acid breakdown actually enter the tricarboxylic acid cycle, which is the "tread mill" over which carbohydrate is known to be oxidized to carbon dioxide and water by the way of pyruvic acid.

Since acetic acid or any of its then known derivatives could not react with oxalacetate to form citric acid and hence enter the cycle, the term "active acetate" was applied to the unidentified substance which allowed this reaction to proceed. Although the structure of CoA was by now fairly clear, Lynen and his coworkers supplied the critical piece of the puzzle (34) when they

isolated a small amount of "active acetate" and demonstrated that it was actually a complex of acetic acid and coenzyme A. This group soon found that "active acetate" is a thiol ester, in which acetate is esterified to the —SH group of coenzyme A, and is called acetyl-CoA (Fig. 4).

FIGURE 4. Acetyl — CoA



This observation naturally clarified the central role that CoA plays as an acetyl group transfer agent, pointed to the —SH group as the active group in the molecule which in turn greatly broadened the scope of importance of this class of compounds ((i.e.) the thiol esters) in biochemical reactions.

In view of the known role of the 2 carbon fragment, acetate, in steroid synthesis the suggestion that pantothenic acid as CoA is important for the synthesis of the adrenal steroid hormones becomes obvious. Evidence that pantothenic acid is actually involved in steroid synthesis was provided by Klein (35, 36) who found both with yeast and with liver slices that CoA favorably influenced the synthesis of both steroids and total lipids.

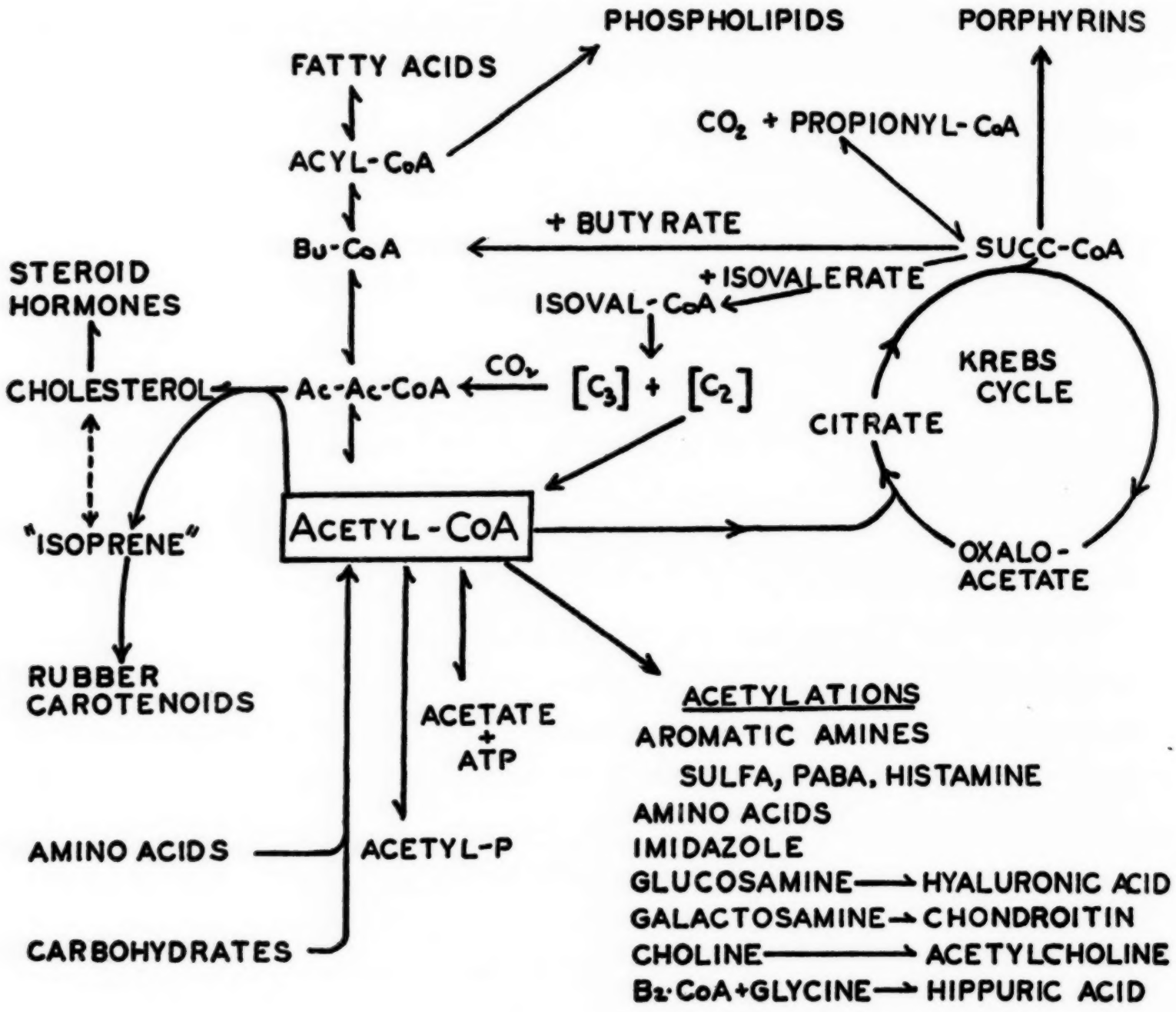
The manifold biochemical reactions involving CoA, and the key, central role that it plays in these numerous metabolic transformations is best illustrated by the information presented in (Fig. 5).

Although it is not possible to correlate with exactness the presence of a given sign of pantothenic acid deficiency with an actual reduced function of coenzyme A for which pantothenic acid is essential, the evidence that has been discussed, such as reduced adrenal steroid activity, evidence of nerve lesions involving acetyl choline, depressed acetylation of such substances as sulfanilamide all implicate the important part played by pantothenic acid in the general physiological economy.

Pantothenic Acid in Human Nutrition

Despite the fact that pantothenic acid deficiency has not been described *per se* in the clinical literature, it seems reasonable to consider it as a required vitamin in view of its well demonstrated biochemical role. The reasons why pantothenic acid deficiencies are not readily seen in human subjects likely relates to the fact that the average daily intake from dietary sources of pantothenic acid may be in the range of 10 to 20 mg. Since pantothenic acid is so widely distributed in natural foods it would indeed be difficult under ordi-

FIGURE 5. The Metabolic Activity of CoA [After Novelli (29)]



nary circumstances to select a diet which would be deficient in this factor. The unusual preparation of foods under acidic or basic conditions could contribute to destruction of pantothenic acid. Adult needs of this vitamin may also be low due to the fact that growth has ceased. It is interesting to contemplate the possible requirement for this vitamin in rapidly growing children as compared to the adult.

Summary

The story of our knowledge of pantothenic acid starts with a lowly yeast cell and has developed gradually, first in the crude stages of animal experimentation, then through the perhaps more critical phases involving attempts to get a clearer picture of its physiological function, until finally today we find in nearly every biochemical laboratory some hotly pursued research dealing with the complex enzymatic function of coenzyme A, the biologically active form of the vitamin.

It is a factor required for growth, for the cellular integrity and function of the adrenal cortex and serves as a key substance which makes possible the intricate transformation of numerous substances within the cell. Starting with the cell and ending with the cell — still with much left to learn.

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NEWS DIGEST

VITAMIN A IN RHEUMATIC FEVER: The observation that the metabolism of vitamin A may be abnormal in rheumatic fever has recently been confirmed and the findings extended according to a report by Jacobs et al (1). Plasma vitamin A levels were determined in 1000 patients with rheumatic fever, and the results were averaged according to arbitrary ranges of body temperature, or according to the time after the commencement of the disease. The authors state that, "No claim can be made either that rheumatic fever differs from other febrile diseases in its effect on vitamin A metabolism, or that vitamin A is the only nutrient affected. The danger that the prolonged course of rheumatic fever may eventually exhaust the vitamin A reserves in the liver, and so produce a conditioned deficiency of vitamin A, should not, however, be ignored.

(1) JACOBS, A. L., Leitner, Z. A., Morre, T., and Sharman, I. M., *J. of Clinical Nutrition 2,* 155 (1954).

FAT SUPPLEMENTS FOR CRITICALLY ILL PATIENTS: From the recent observations of Mindriem (1) it is evident that "the use of fat supplements to provide high caloric intake is of value in the management of malnutrition and its complications occurring during protracted illness." The supplements used were mainly fat emulsions given by stomach tube. "One type of mixture found to be well tolerated consisted of 50 per cent oil, (edible oil such as salad oil), 12 per cent sucrose, 2 per cent emulsifying agent, vanilla flavor and water. Such an emulsion furnishes 5.1 calories per lb. It can be further fortified by adding skim milk powder. Twenty-three gm. of skim milk powder added to the mixture does not greatly change the volume, but adds much to palatability, protein content, and calories." When this form of fat emulsion was given to provide supplemental calories to nine critically ill patients who evidenced signs of protein depletion, marked improvement was observed "as shown by sense of well-being, weight gain, increased resistance to infection, and accelerated rate of wound healing."

(1) MINDRIEM, Gordon M., *J. Clinical Nutrition 1,* 503 (1953).

ESSENTIAL FATTY ACIDS AND HUMAN NUTRITION: In several papers published in the *Journal of Nutrition,* Hansen and Wiese (1, 2) report that healthy infants and children maintain relatively high serum levels for linoleic and arachidonic acids. "On a dietary intake comprising about 3 per cent of the total calories as linoleic acid, the mean serum levels of 2, 3, and 4 double-bond fatty acids for 60 healthy control children

4 to 15 years of age were, respectively 30.3, 1.5 and 10.2 per cent of the total fatty acids." The author also carried out blood serum analyses on 57 poorly-nourished infants and children for the total fatty acids, dienoic, trienoic, tetranoic, and hexaenoic acids. "There were no signicant differences in the amount of total fatty acids in serum of children in fair and poor nutritional states as compared with well nourished children. Dienoic, tetraenoic, and hexaenoic acid levels in the serum of inadequately nourished children were significantly lower than in healthy children. The trienoic acid level in the serum of inadequately nourished children was significantly higher than in healthy children."

(1) WIESE, H. F., Gibbs, R. H., and Hansen, A. E., *J. Nutrition 52,* 355 (1954).
(2) HANSEN, A. E., and Wiese, H. F., *J. Nutrition 52,* 367 (1954).

X-IRRADIATION PROTECTION BY LINOLEIC ACID: Earlier work had demonstrated that diets containing 2 per cent of cottonseed oil exerted a beneficial effect against X-irradiation in rats. In other experiments oats supplemented with only 10 mg. of methyllinoleate were similarly protected. Because of these observations Devel and co-workers conducted a study to find out "whether or not the protective action of essential fatty acids is related to the amount ingested in the same manner as growth is related to this factor, or whether only catalytic amounts are required to initiate this action" (1).

"On the basis of the average length of survival, and from comparison of the periods required for LD_{25}, LD_{50}, and LD_{75} to be reached in male rats subjected to X-irradiation, it was demonstrated that the protective effect of ethyl linoleate became greater with increasing dosage."

The optimum protective dosage level of ethyl linoleate "probably exceeds 100 mg. per day."

(1) CHENG, A. L. S., Ryan, M., Alfin-Slater, R., and Devel, Jr., H. J., *J. Nutrition 52,* 637 (1954).